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## ADENOVIRUS INFECTIONS IN CHILDREN

[Following is a translation of an article in French by Ch. Chany of the Virus Research Center, Saint Vincent de Paul Hospital, Paris, in the German-language periodical Archiv für die gesamte Virusforschung (Archives for General Virus Research), No 13, 1963, pages 294-301.]

### Introduction

The isolation of adenoviruses in 1953 by Rowe and his associates constituted an important event in the history of respiratory diseases of viral origin. After the work on poliomyelitis, the study of respiratory viruses was the first to profit by the new cell culture methods. But the isolation of this group of viruses had another, important interest for pathology, which is only now being revealed.

The work of Rowe and others (1) showed that the cell culture method permits the discovery of viruses persisting in the tissues in a latent state. In fact, cultures of amygdalian cells reveal adenoviruses, while extracts of these same amygdalae, introduced in cell culture by inoculation do not, as a general rule, permit isolation.

### Definition

The virus develops inside the nucleus, undergoing under the optical microscope characteristic nuclear changes specifically connected with the adenoviruses (2,3,4,5,6). The precocious lesions are negative Feulgen eosinophile inclusions. In the more advanced stages of evolution, the nucleus is more and more loaded with a basophilic material rich in DNA (deoxyribonucleic acid), forming a central inclusion surrounded by a clear zone, constricted in places, the whole taking on the henceforward classical rose-pink aspect. The eosinophile inclusions correspond to protein crystals; the basophilic inclusions contain viral particles.

In electronic microscopy the viral particles are found to be grouped in a crystalline formation (7,8). The diameter of a particle is approximately from 80 to 100 millimicrons. The virion is made up of a 2,3,5 cubic symmetry capsule (capside) composed of 252 subunits or capsomeres (9). The genetic material of the virus is deoxyribonucleic acid. In the cells, the viruses of this group produce proteins, one of which constitutes the antigen deviating the complement common to this group (10). Another of these proteins is the cell-separating factor (11,12) characteristic of the adenoviruses. According to their type, the adenoviruses hemagglutinate

human red corpuscles as well as those of the monkey, the mouse, and/or the rat (13). Inhibition of hemagglutination permits the type classification of adenoviruses. This reaction can also be utilized to reveal the antibodies inhibiting hemagglutination in infected subjects (14).

The antigenic properties of the shell enable us to distinguish 28 different types of adenoviruses that may be revealed through neutralization reactions with the help of a specific immune serum. As the capsule (capside) contains no lipid components, adenoviruses are resistant to ether.

Adenoviruses have been isolated in man as well as in animals (monkey (15), dog (16), and owl).

Clinically, the adenoviruses can produce acute and chronic infections.

#### A. Clinical Manifestations Observed in Acute Infections

A very large number of infections may occur without any clinical symptoms. They may be associated with or accompanied by minor manifestations which may pass virtually unnoticed. The existence of unapparent infections must always be taken into consideration in evaluating epidemiological investigations.

The virus is usually isolated from pharyngeal secretions or from stools. Recently, Gresser and Kibrick isolated this virus also from urine (17).

Diagnosis is based on the isolation of the virus and on the significant rise in antibodies (establishing the complement, neutralizing or inhibiting hemagglutination) by comparing the serums taken at the acute stage of the disease and at the period of convalescence. The relations between infection and clinical manifestations depend on statistical data, as Dr. Svedmyr has noted.

##### 1) Manifestations commonly observed in adults and children

Pharyngitis is virtually constant and presents no characteristic symptom. The pharynx is red and congested, with occasional hyperplasia of the lymphoid tissues. The amygdalae may be large and the seat of small whitish elements. In the absence of super-infection, there is no exudation. This pharyngitis is sometimes accompanied by adenopathy in the companion area.

Conjunctivitis is observed in isolation or associated with pharyngitis. Generally it begins on one side, settling on the conjunctiva and the sclera, especially at the level of the interior angle of the eye. It

may be accompanied by edema. The conjunctiva is congested, may show some follicular elements and be accompanied by a sensation of the presence of a foreign body. Corneal opacities may appear in the period of convalescence, persisting in some cases for years and disturbing vision. Conjunctivitis has been observed by Jawetz and his collaborators in association with adenovirus type 8, and occurring principally under certain conditions, particularly in workers in naval construction plants (18).

Pharyngo-conjunctival fever has most often been observed in association with adenovirus type 3 (19).

Conjunctivitis has been reproduced experimentally with volunteers when the conjunctiva has been mechanically irritated prior to inoculation with the virus. Simple instillation of the virus does not enable us to reproduce the disease (20). A prior traumatism of the tissues therefore seems to be necessary, either for the penetration of the virus or to permit its proliferation. We can assume that dusts may play such a role under certain conditions. This is apparently the case in the naval construction plants mentioned above.

Respiratory manifestations. These occur especially in certain communities, such as hospitals (21,22), vacation camps, and military training camps (23). They may also occur in family surroundings. They spread relatively little and build limited epidemic foci. They are accompanied by a fever with wide oscillations, dropping in the morning and rising again in the evening. This fever may reach as high as 39° to 40°. Coughing is often severe and paroxysmal. Bronchial affection may be revealed by radiological examination in the form of lobar opacities, which are probably due particularly to disturbances in ventilation. When the seat of lesion is juxta-cortical, the affection may also be parenchymatous, with monocyte pleural effusion.

Gastro-intestinal manifestations. These are of rather considerable frequency, with abdominal pains, vomiting and diarrhea. It is appropriate in this connection to recall the observations of Kjellen, who isolated adenoviruses from cultures of mesenteric ganglia during acute mesenteric adenitis.

Cutaneous manifestations. Transitory morbilliform eruptions without secondary desquamation have been observed on the face, neck, and thorax (21, 26). Diagnostic problems are furthermore complicated by the fact that adenovirus infections may perfectly well occur during convalescence from measles.

Although the prognosis for adenovirus infections is usually favorable, especially in countries with a high living standard, it is quite otherwise in certain underprivileged communities or countries with a low living standard.

## 2) More uncommon clinical manifestations

Severe adenovirus pneumonia in children. Literature on this subject has reported severe or fatal manifestations, accompanied by a train of symptoms not usually observed in adenovirus affections. In 29 cases of serious adenovirus attacks, studied from 1955 to 1961 in the Saint Vincent de Paul Group, Department of Prof. Lelong, the incidence of various clinical manifestations is summarized in Table 1:

Table 1. Clinical manifestations observed in 20 cases of severe adenovirus pneumonia in the Paris region 1955-1962.

Pulmonary manifestations	29
Cutaneous manifestations, morbilliform eruptions	6/29
Severe digestive manifestations, bloody diarrhea	7/29
Heart failure	2/29
Nervous manifestations -- paresis, with symptoms of pyramidal affections, convulsions, coma	6/29
Severe electroencephalographic disturbances (2 cases transitory and regressive)	4/29
Acute nephritis	5/29

It is interesting to note in this table the relatively high incidence of severe electroencephalographic disturbances which may be transitory and regressive. In parallel fashion, the incidence of renal manifestations seems relatively high.

The severity of certain adenovirus epidemics was also reported by a Chinese author during the great Peiping epidemic of 1958. Table 2 summarizes this author's observations. Out of 3,398 cases of severe pneumonia, 528 were fatal, autopsy was made in 110 cases, and adenovirus pneumonia lesions were observed 92 times. Of 84 pulmonary cases, adenoviruses of type 3 or 7 were isolated 57 times, while myxoviruses were isolated only 18 times (3 stocks of Asian flu A<sub>2</sub>, 15 stocks of myxovirus parainfluenza 1 Sendai). A high incidence of nervous manifestations during this epidemic was also reported.

Table 2. Peiping epidemic of 1958, reported by Teng Chin-Hsien

Total	3,398
Fatal pneumonia	528
Autopsies	110
Characteristic adenovirus lesions	92
Isolation of adenovirus type 3, 7	57
Myxovirus	18

#### Anatomic aspects of adenovirus pneumonia

a) The anatomic lesions are characteristically pulmonary.

It was Goodpasture and others (31) who drew attention to the

peculiar aspect of these lesions in 1939. However, at that time they were not able to pinpoint the virus involved.

In 1955, in Prof. Lelong's department, in association with Le Tan Vinh and Satge, by isolating the virus and by an anatomical study we were able to identify the pneumonia described by Goodpasture as adenovirus pneumonia.

This pneumonia is characterized:

1) by necrotic lesions predominating in the bronchia and affecting the ciliated epithelium; these lesions may spread to the pulmonary parenchyma;

2) by the presence of cells with a swollen nucleus containing an eosinophile or basophilic inclusion surrounded by clear vacuoles; these inclusions spare the nucleolus, and are thus distinguished from the herpetic lesions;

3) by localization of the specific lung lesions; the isolated viruses in these cases were usually of type 7, occasionally of type 3.

b) Congestive non-specific lesions have been reported by a number of authors. In this case no focus of necrosis is found. It seems probable that in most of these cases, the cause of death is not connected with the adenoviruses, but with another associated affection.

#### B. Chronic Adenovirus Infections

Although acute adenovirus infections have been relatively well studied, our knowledge of chronic adenovirus infections is certainly still very fragmentary. In the introduction we insisted on the importance of exposing latent viruses by cell culture. Adenoviruses, particularly types 1, 2, 5, 6 may persist for a very long time in the amygdalae and adenoids without our being very sure under what form. Recently the hypothesis was expressed that interferon would be capable of intervening in the maintenance of chronic infection (32, 33, 34, 35).

Experimental cell culture patterns have been produced in vitro by a great number of authors. It has been observed that a real balance exists between viral multiplication and interferon production in certain systems.

However interesting these experimental patterns may be, it is difficult to draw an analogy between the systems studied in vitro and happenings observed in vivo. In the systems chronically infected in vitro, the production of interferon is closely connected with viral multiplication, and there is no proof that the adenoviruses multiply constantly or intermittently in the amygdalae. Moreover, the adenoviruses do not seem to be

very sensitive to the action of interferon.

Although little understood, the problem of chronic adenovirus infections has great interest from the theoretical point of view.

A recent American report by J. J. Trentin, Yabe and Taylor (35) makes one of the adenoviruses, type 12, a responsible agent in the cancerous transformations of cells. This virus, given to a baby hamster by intrapulmonary inoculation, produced tumors in the thorax in 41 out of 45 cases, with the tumors spreading to the liver in 6 cases.

If this work is confirmed, this important observation could supply a new stimulus to the study of adenoviruses. We may conclude from this study that the pathogenic action of the viruses in the organism is often unforeseeable, and that in fact adenoviruses are as much respiratory as they are enteric viruses, and are perhaps even oncogenic viruses. Viruses may not be defined in terms of the organ in which they multiply or in terms of lesions in the tissues. Likewise, they may not be defined by the clinical manifestations they produce. What defines the virus is the morphological structure of the particle and the chemical and antigenic nature of its constituents.

#### Summary

Adenoviruses may be defined as follows:

1) They form a group of viruses which carry out characteristic nuclear changes in cell structure.

2) The diameter of the viral particles is from 80 to 100 millimicrons. The particle is made up of a capsule (capside) of 2, 3, 5 cubic symmetry and of 252 capsomeres.

All adenoviruses produce an antigen deviating the specific complement of the group. With the help of neutralization reactions and by inhibiting hemagglutination we may distinguish 28 types of adenoviruses.

Clinically, the adenoviruses may produce acute and chronic infections.

The acute infections are now quite well known and have been schematically presented in this report.

The manifestations usually observed are:

1) conjunctivitis; 2) pharyngo-conjunctival syndroms, 3) isolated pharyngitis, 4) atypical pneumonia without cold agglutinins, 5) morbilliform eruptions.

Infantile pneumonia may in certain cases be accompanied by encephalic



and renal manifestations. The evolution may be severe, sometimes fatal. Anatomic lesions are essentially pulmonary. In typical cases necrotic pneumonia with inclusions is involved.

On the other hand, the chronic infections are little understood.

In the first isolations of adenoviruses, it was demonstrated that these viruses may persist a long time in the organism in a latent state, particularly in the lymphoid tissues. The form and conditions of persistence of the virus in the tissues are not known.

A recent study attributes a cancerous role in the baby hamster to adenovirus type 12. ( )

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